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ORIGINAL RESEARCH

Clozapine and Neutropenia in Patients with Schizophrenia and SARS-CoV-2 Infection

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Background: Clozapine (CLZ) is used for treatment-resistant schizophrenia (TRS). Adverse reactions to clozapine include neutropenia. In March 2020, WHO declared the COVID-19 pandemic and after, psychiatrists raised concerns regarding continuation of clozapine, due to multiple restrictions. We aimed to provide a study on the association between neutropenia and clozapine in patients with schizophrenia and COVID-19.

Aim: To assess the neutrophil count in patients with schizophrenia treated with clozapine and infected with COVID-19.

Methods: The study patients with schizophrenia, according to DSM-5, admitted to the Clinical Hospital of Psychiatry and Neurology Brasov, Romania, between April 2020 and October 2021. The inclusion criteria included positive RT-PCR (real-time PCR) test for COVID-19 and treatment with clozapine. We assessed three values of ANC (absolute neutrophil count): before COVID-19 infection (last ANC obtained at mandatory check), during infection and 1 month after resolution (first negative PCR test).

Results: Of the 105 cases, 95 did not have neutropenia. Fifty-nine patients were males (62.1%), mean age was 43.5 years (SD = 12.1) with an average of clozapine treatment of 52.4 months (SD = 11.9). At baseline, they had a small reduction in the ANC mean value (4.41 × 109/l; SD = 2.22) which did not constitute a statistically significant decline from the prior to COVID-19 mean value of 4.66 × 109/l (SD = 2.34; p = 0.45). Values were also normal in the first month after negative PCR testing (4.45 × 109/l; SD = 2.35; p = 0.91). A total of 10 patients (9.5%) had neutropenia. The age, dose of clozapine and duration of treatment were not statistically different compared to the group without neutropenia.

Conclusion: Psychiatrists and other health professionals should keep in mind that neutrophil count may decrease during COVID-19 infection in patients taking clozapine and in some cases, neutropenia may even occur. We assumed that neutropenia could be caused by COVID-19 and clozapine interaction.

Keywords: clozapine, SARS-CoV-2, schizophrenia, agranulocytosis, neutropenia

Introduction

Clozapine (CLZ) remains the gold standard for patients with treatment-resistant schizophrenia (TRS).[1] In many cases, it is also used in severe manic episode[2] and for its anti-aggressive anti-suicidal properties in schizophrenia, bipolar disorder, personality disorder, intellectual disability, dementia, etc.[3] Rare but serious side effects such as agranulocytosis, seizures, myocarditis and orthostatic hypotension and increased mortality in elderly patients with dementia (clozapine black box warnings) cause the underuse of clozapine even where it is strongly indicated.[4]

The SARS-CoV-2 pandemic that was declared in March 2020 has had a major impact on mental health, especially in patients with schizophrenia.[5] Lockdown, social isolation, difficulties to contact psychiatrists, GPs and limited or restricted access to hospitals have led to an increase in morbidity and mortality in this group of patients.[6] In a recently published paper, we noticed that patients who received adequate treatment and care in dedicated wards appeared to be protected from severe forms of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[7] Other authors have suggested that COVID-19 associated with inflammation may accelerate clozapine toxicity.[8]

Due to the nature of the treatment, clozapine requires white blood cell and neutrophils monitoring in order to avoid potentially dangerous situations (neutropenia).[9] Neutropenia is defined as an absolute neutrophil count (ANC) of less

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than 1500/μL. It could be mild (between 1000/μL and 1500/μL), moderate (between 500/μL and 1000/μL), or severe (less than 500/μL).[10] It has a variety of causes, such as viral infections, medications, therapeutic radiation, autoimmune disorders, malignant diseases, nutritional deficiencies, congenital causes and others.[11]

A particular congenital cause of neutropenia is benign ethnic neutropenia (BEN), one of the most common causes of chronic neutropenia in members of some ethnic groups, mainly African, Caribbean, Middle Eastern and West Indian, without any increased risk of infection.[12] This condition is important for patients receiving therapies that have neutropenia as a side effect, such as clozapine. In this context, the experts proposed guidelines for the continuation of clozapine treatment during the pandemic.[13] On the other hand, the interaction between antivirals that act as protease inhibitors (nirmatrelvir and ritonavir combination) and clozapine may lead to an increase in antipsychotic plasma concentration and should therefore be closely monitored.[13]

Aims

We aimed to evaluate the ANC in a group of patients with schizophrenia treated with clozapine. The study's methodology was approved by the local hospital ethics committee.

Materials and Methods

Study Design and Setting

We collected data from clinical records of patients diagnosed with schizophrenia according to DSM-5, treated with clozapine and tested positive for SARS-CoV-2 using PCR method. These patients had a pre-infection CBC (complete blood count) – a procedure according to clozapine treatment guidelines; CBC was performed during hospitalization for COVID-19 infection (baseline) and 1 month after the first negative PCR test which confirmed viral infection resolution. The clinical tests were conducted at the Clinical Hospital of Psychiatry and Neurology in Brasov between April 2020 and October 2021. This hospital is an academic setting with a total of 450 beds, for both acute patients (150 beds) and for chronic psychiatric patients (300 beds). Since April 2020 the hospital was declared COVID-19 support-hospital, with 90 beds for treating COVID-19 positive cases.

The evaluation was performed by three board-certified psychiatrists and one specialist in laboratory medicine with experience in clinical research. Demographics included age, gender, duration of illness, duration of clozapine treatment, and dose of clozapine. We compared the mean values for ANC, lymphocyte count and WCC for three sets of data: before COVID-19 infection vs baseline; baseline vs post-COVID-19 infection; before vs after COVID-19 infection. According to the hospital's protocols, all blood samples for laboratory analyses were collected in the morning on empty stomach. All samples were peripheral venous blood collected in standardized kits. SARS-CoV-2 infection was confirmed using 2 consecutive Polymerase Chain Reaction (PCR) tests (day 1 and day 5) performed by a specialist in laboratory medicine.

Data Analysis

Results were analyzed using SPSS program version 20.00. The adjusted odds ratio (AOR) with 95% CI was calculated and p-values less than 0.05 using *t*-test method. The multivariable logistic regression was considered to indicate a significant association.

Results

The study included a total of 105 patients. Of the 95 cases without neutropenia, 59 patients were males (62.1%); mean age in this group was 43.5 years (SD = 12.1) with an average duration of clozapine treatment of 52.4 months (SD = 11.9) (range 2 years to 12 years). At baseline, they had a small reduction in the ANC mean value (4.41×10^9/l; SD = 2.22) which did not constitute a statistically significant decline from the prior to COVID-19 mean value of 4.66×10^9/l (SD = 2.34; p=0.45). ANC values were also normal in the first month after negative PCR testing (4.45×10^9/l; SD = 2.35; p=0.91). Twenty-one patients were from the chronic ward, 44 patients from the acute ward and 40 from the outpatient department. There were no deaths registered during the COVID-19 hospitalization. Patient characteristics are described in Table 1.

Table 1 Patient's Characteristics

Characteristics		No Neutropenia Group	Neutropenia Group	*p* value
		N = 95	N = 10	
Age	Mean (SD)	43.5 (12.1)	45.7 (7.8)	0.57
Male		59 (62.1%)	6 (60%)	0.89
Clozapine duration (months)	Mean (SD)	52.4 (11.9)	46 (12.1)	0.11
Clozapine dose for acute patients (mg) n = 44	Mean (SD)	325 (246)	311 (212)	0.86
Clozapine dose for chronic patients (mg) n = 21	Mean (SD)	241 (103.2)	300 (50)	0.08
Clozapine dose for outpatients (mg) n = 40	Mean (SD)	220 (120.2)	243 (115.8)	0.56
Length of stay in Covid-19 unit (days)	Mean (SD)	14.12 (1.6)	18.23 (2.3)	0.001
Severity of Covid-19 infection	Mild	88; 92.6%	7; 70%	0.02
	Moderate	6; 6.3%	2; 20%	0.12
	Severe	1; 1.1%	1; 10%	0.06
Smoking		63; 60%	7; 70%	0.53
Comorbidities	Respiratory	15; 15.8%	3; 30%	0.25
	Cardiovascular	20; 21.1%	2; 20%	0.93
	Metabolic	28; 29.5%	3; 30%	0.49
	Neurological	3; 3.1%	1; 10%	0.08
	Others	11; 11.6%	1; 10%	0.88
	Without	18; 18.9%	0; 0%	0.13
Deaths		0; 0%	0; 0%	-

Clozapine doses were significantly higher in acute patients than in outpatients (325 ± 246 mg, vs 220 ±120.2 mg, p = 0.03). Blood parameters are presented in Table 2.

Baseline neutropenia was identified in 10 cases (Table 3). In 9 cases, neutropenia was mild (1.0–1.5 × 10^9/L), and in one case, it was moderate (0.76 × 10^9/L) leading to discontinuation of clozapine and switching to another antipsychotic.

Table 2 Blood Parameters During Evaluation of Patients without Neutropenia (n = 95)

Parameter	Prior Covid-19 Infection (Before 1st Positive PCR Test)	Baseline (1st Positive PCR Test)	After Covid-19 Infection (After 1st Negative PCR Test	*p* value Prior Infection vs Baseline	*p* value Baseline vs After Infection
WBC mean; SD; (min and max)	7.33; 2.76; 3.41–16.22	7.28; 2.45; 2.85–15.79	7.11; 2.73; 3.11–15.33	0.56	0.78
Neutrophils mean; SD; (min and max)	4.66; 2.34; 0.73–12.56	4.41; 2.22; 0.72–12.98	4.45; 2.35; 0.76–14.21	0.45	0.91
Lymphocyte mean; SD; (min and max)	1.78; 0.73; 0.5–3.74	1.73; 0.74; 0.5–3.56	1.75; 0.73; 0.6–3.21	0.63	0.77

Table 3 Blood Parameters During Evaluation of Patients with Neutropenia (n = 10)

Parameter	Prior Covid-19 Infection (Before 1st Positive PCR Test)	Baseline (1st Positive PCR Test)	After Covid-19 Infection (1st Negative PCR Test	p value prior Infection vs Baseline	p value Before Infection vs After Infection
WBC mean; SD; (min and max)	7.14; 2.51; 3.47–13.61	3.91; 1.57; 2.41–5.55	6.12; 2.48; 3.55–16.03	0.002	0.37
Neutrophils mean; SD; (min and max)	4.48; 2.30; 0.76–12,43	1.51; 0.64; 0.72–1.91	4.76; 2.25; 1.7–12.44	0.001	0.78
Lymphocyte mean; SD; (min and max)	2.0; 0.78; 0.64–3.74	1.69; 0.68; 1.7–3.46	1.77; 0.65; 0.5–3.64	0.35	0.49

COVID-19 symptoms were mild (only 2 cases of moderate symptoms). Switching medication caused relapse in 7 (70%) leading to prolongation of hospitalization compared to those without neutropenia.

According to the local protocol, patients were treated with hydroxychloroquine, lopinavir/ritonavir azithromycin, and enoxaparin. Patients were not treated with monoclonal antibodies, and none were vaccinated against COVID-19 at the time of evaluation. The number of patients requiring oxygen therapy was small.

Discussion

Our study shows data of neutrophil counts in a group of patients treated with clozapine with evidence of pre-pandemic ANC values. Previous studies have shown a reduction in neutrophil counts in patients treated with clozapine and infected with COVID-19. Neutropenia can occur in many situations including BEN (benign ethnic neutropenia). No such cases have been identified in our patients. For BEN patients who are on clozapine, Manu et al described that the frequency and severity of infections were similar to others on the same medication, despite the difference in ANC.[14]

A neutrophil count >1000/μL is safe for initiating and/or resuming clozapine therapy, and it should be discontinued only when the ANC falls below 500 μL for those who have BEN.[15]

Another particular cause of neutropenia is the infection with SARS-CoV-2 virus. The COVID-19 pandemic has also raised issues for patients treated with clozapine because clozapine is associated with an increased risk of pneumonia (higher rates of smoking, cardiovascular disease, respiratory disease, diabetes and chronic renal failure),[16] weight gain, the reduction in immunoglobulins, neutropenia (usually in the first 18 weeks) and progression to agranulocytosis (in a minority of cases). Recently published data suggest that patients treated with clozapine are at increased risk for COVID-19.[17] Gee and Taylor, in a retrospective chart review study, showed a significant reduction in ANCs, lymphocyte counts and total WCCs in the week after a positive SARS-CoV-2 test result. They suggest that mild neutropenia in the acute phase of COVID-19 illness in patients who are well established in clozapine is more likely to be a consequence of the infection than related to clozapine treatment and the rapid return to baseline counts supports this conclusion.[18] Our research included only white individuals and it partially confirmed the results reported by Gee and Taylor on a larger sample. In this respect, we have observed that about 10% of patients on clozapine who were COVID infected had significant neutropenia. This is more than double the expected rate (3.8% in Myles 2018)[19] and, even more importantly, has been found in patients on long-term clozapine treatment. In our clinic, the percentage of cases of neutropenia is below 1%.

There are 4 possible explanations for this finding: a) it could be a late adverse effect of clozapine – very unlikely; b) it could be a consequence of COVID 19 infection by itself – unlikely, given very small (relatively) number of case reports; c) it could be produced by other medications/diseases – possible, but much more research will be necessary; d) it could be produced by the COVID virus in patients taking clozapine – probable, and the most interesting finding since the patients were on this type of treatment for more than 18 months and the ANC were normal before coronavirus infection. This group did not differ from the rest of the patients in terms of age (older but not significant), dose of clozapine or

treatment duration, although we noticed more metabolic comorbidities and anemia. However, their evolution was complicated by the switch from clozapine to another antipsychotic along with other possible causes (COVID-19 infection, hospitalization-associated infections, experimental treatments, etc.).

Clozapine cessation could have severe consequences (relapse, hospitalization, prolongation of admission, and severe stress for patient and family). In our study, patients switched from clozapine relapsed with prolongation of hospitalization. Mandatory WCC (white cell count) daily monitoring (including ANC) has been an effective strategy for mitigating this risk because mild-to-moderate neutropenia does not increase the risk of infection.[20]

Data suggest that COVID-19 infection can cause transient mild neutropenia and this is not purely clozapine induced. Patients who have been taking clozapine for more than 6 months and have not had previous episodes of neutropenia should continue treatment even if their ANC drops below 1.5×10^9 /L during the period of COVID-19 illness.[17] Cranshaw and Harikumar[21] presented a case of clozapine toxicity in relation to COVID-19, with concurrent mild and transient neutropenia. Luykx et al[22] described a case of a patient who was taking clozapine and developed "severe neutropenia", while he had COVID-19. In a recent paper, Dotson et al[23] showed clozapine toxicity in 3 cases of patients treated with clozapine, while they had COVID-19, one of whom also experienced neutropenia. Gee and Taylor suggest that mild neutropenia in the acute phase of COVID-19 in patients who are well established in clozapine, is more likely to be a consequence of the virus than of clozapine treatment.[24] In essence, all these results show that patients with COVID-19 and clozapine treatment registered an initial decline in the ANC value by 17% but subsequently it increased to around 95% of the pre-infection value due to the resolution of the infection.[25]

For patients treated with clozapine who develop COVID-19, Gee and Taylor suggest continuing clozapine when it is possible (even during ventilation), reducing the dose if necessary in relation to blood results and cease if there is a significant fall in neutrophils (COVID-19 is linked to lymphopenia but not neutropenia).[26] All this aims to prevent relapse due to untimely changes in clozapine, a fact confirmed by our results. Furthermore, for protection against the severity of respiratory infection, they also recommend adding vitamin D to all clozapine patients, since psychotic patients are at high risk of vitamin D deficiency. In one study from the United Kingdom, about half of the psychotic patients were vitamin D deficient.[27]

The study has some limitations. One of them could be the relatively small number of patients. Another limitation could be the limited data regarding antipsychotic adherence before COVID-19 infection in outpatients. The novelty of the study resides in comparing the pre-pandemic laboratory values to those obtained during COVID-19 infection and in the post-infection period. Results led us to conclude that the ANC reduction was temporary and most likely caused by the viral infection and not by clozapine. Future analysis of patients with schizophrenia treated with antipsychotics and infected with COVID-19 may provide new information on whether this virus may cause a decrease in ANC independently of clozapine treatment.

Conclusion

COVID-19 could be associated with a temporary reduction in ANC levels, which is mild, transient and not statistically significant in the vast majority of patients, including those treated with clozapine. We identified neutropenia in a small group of patients, and we assumed that it was caused by the coronavirus infection and clozapine interaction. Clozapine discontinuation could generate relapse, with severe consequences for patients and their families. It is opportune to continue the administration of clozapine for patients who are stable in this treatment.

Abbreviations

CLZ, clozapine; TRS, treatment-resistant schizophrenia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease; ANC, absolute neutrophil count; BEN, benign ethnic neutropenia; PCR, Polymerase Chain Reaction; CBC, complete blood count; AOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation.

Data Sharing Statement

Anonymised participant data could be made available, upon requests directed to the corresponding author.

Ethical Approval and Consent to Participate

Ethical clearance was secured by the Ethical Committee of Clinical Hospital of Psychiatry and Neurology of Brasov, Romania. Informed written consent was taken. Confidentiality of the information was maintained, and the data were recorded anonymously throughout the study. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–796.
2. Ifteni P, Correll CU, Nielsen J, Burtea V, Kane JM, Manu P. Rapid clozapine titration in treatment-refractory bipolar disorder. *J Affect Disord*. 2014;166:168–172. PMID: 25012427. doi:10.1016/j.jad.2014.04.020
3. Andreea T, Petru I, Miron AA, Paula-Simina P, Lorena D. Clozapine for treatment-refractory aggressive behavior. *Psychiatr Q*. 2021;92 (2):721–733. PMID: 32918660. doi:10.1007/s11126-020-09839-x
4. Lieberman JA. Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry*. 1998;59(Suppl 3):38–43. PMID: 9541337.
5. Kozloff N, Mulsant BH, Stergiopoulos V, Voineskos AN. The COVID-19 global pandemic: implications for people with schizophrenia and related disorders. *Schizophr Bull*. 2020;46(4):752–757. PMID: 32343342; PMCID: PMC7197583. doi:10.1093/schbul/sbaa051
6. Ifteni P, Dima L, Teodorescu A. Long-acting injectable antipsychotics treatment during COVID-19 pandemic - A new challenge. *Schizophr Res*. 2020;220:265–266. PMID: 32349886; PMCID: PMC7185008. doi:10.1016/j.schres.2020.04.030
7. Moga S, Teodorescu A, Ifteni P, Gavris C, Petric PS. Inflammatory response in SARS-CoV-2 infection of patients with schizophrenia and long-term antipsychotic treatment. *Neuropsychiatr Dis Treat*. 2021;17:3053–3060. PMID: 34629871; PMCID: PMC8495225. doi:10.2147/NDT.S325062
8. Butler M, Bano F, Calcia M, McMullen I. Clozapine prescribing in COVID-19 positive medical inpatients: a case series. *Ther Adv Psychopharmacol*. 2020;10:2045125320959560. PMCID: PMC7493264 PMID: 32974002. doi:10.1177/2045125320959560
9. Schulte P. What is an adequate trial with clozapine?: therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. *Clin Pharmacokinet*. 2003;42(7):607–618. PMID: 12844323. doi:10.2165/00003088-200342070-00001
10. Hsieh MM, Everhart JE, Byrd-holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. *Ann Intern Med*. 2007;146(7):486–492. PubMed: 17404350. doi:10.7326/0003-4819-146-7-200704030-00004
11. Newburger PE. Autoimmune and other acquired neutropenias. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):38–42. PubMed: 27913460. doi:10.1182/asheducation-2016.1.38
12. Hershman D, Weinberg M, Rosner Z, et al. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. *J Natl Cancer Inst*. 2003;95(20):1545–1548. PubMed: 14559877. doi:10.1093/jnci/djg073
13. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. *J Psychiatry Neurosci*. 2020;45 (3):222–223. PMID: 32297722; PMCID: PMC7828973. doi:10.1503/jpn.200061
14. Manu P, Sarvaiya N, Rogozea LM, Kane JM, Correll CU. Benign ethnic neutropenia and clozapine use: a systematic review of the evidence and treatment recommendations. *J Clin Psychiatry*. 2016;77(7):e909–16. PubMed: 27464332. doi:10.4088/JCP.15r10085
15. Atallah-Yunes SA, Ready A, Newburger PE. Benign ethnic neutropenia. *Blood Rev*. 2019;37:100586. doi:10.1016/j.blre.2019.06.003
16. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013;68 (11):1057–1065. doi:10.1136/thoraxjnl-2013-204282
17. Govind R, Fonseca de Freitas D, Pritchard M, et al. Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. *Br J Psychiatry*. 2020. doi:10.1192/bjp.2020.151
18. Gee S, Taylor D. COVID-19 infection causes a reduction in neutrophil counts in patients taking clozapine. *J Psychiatry Neurosci*. 2021;46(2): E232–E237. doi:10.1503/jpn.200208
19. Myles N, Myles H, Xia S, et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand*. 2018;138 (2):101–109. doi:10.1111/acps.12898
20. Meyer N, Gee S, Whiskey E, et al. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *J Clin Psychiatry*. 2015;76(11):e1410–e1416. doi:10.4088/JCP.14m09326

21. Cranshaw T, Harikumar T. COVID-19 Infection may cause clozapine intoxication: case report and discussion. *Schizophr Bull*. 2020;46(4):751. doi:10.1093/schbul/sbaa070
22. Luykx JJ, van Veen SMP, Risselada A, et al. Safe and informed prescribing of psychotropic medication during the COVID-19 pandemic. *Br J Psychiatry*. 2020;217:471–474. doi:10.1192/bjp.2020.92
23. Dotson S, Hartvigsen N, Wesner T, et al. Clozapine toxicity in the setting of COVID-19. *Psychosomatics*. 2020;61:577–578. doi:10.1016/j.psym.2020.05.025
24. Gee S, Taylor D. The effect of COVID-19 on absolute neutrophil counts in patients taking clozapine. *Ther Adv Psychopharmacol*. 2021;10:2045125320940935. doi:10.1177/2045125320940935
25. Bonaccorso S, Ricciardi A, Ouabbou S, et al. Clozapine, neutropenia and Covid-19: should clinicians be concerned? 3 months report. *Brain Behav Immun*. 2021;13:100212. doi:10.1016/j.bbih.2021.100212
26. Gee S, Gaughran F, MacCabe J, Shergill S, Whiskey E, Taylor D. Management of clozapine treatment during the COVID-19 pandemic. *Ther Adv Psychopharmacol*. 2020;10:2045125320928167. doi:10.1177/2045125320928167
27. Lally J, Gardner-Sood P, Firdosi M, et al. Clinical correlates of vitamin D deficiency in established psychosis. *BMC Psychiatry*. 2016;16(1):76. doi:10.1186/s12888-016-0780-2